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(54) Title: USING COMBINATION OF ESTROGEN AND PROGESTIN WITH ULTRA LOW DOSE FOR LONG TERM ORAL CONTRACEPTION

(57) Abstract: A method for female oral contraception involves administering a combination of estrogen and progestin for 180-364 consecutive days following by non-administration for a period of 3-5 days maximum. An ultra low dose of the estrogen and progestin will be used. The daily amounts of estrogen and progestin are equivalent to about 5-35 mcg of ethinyl estradiol and about 0.050



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## Using combination of estrogen and progestin with ultra low dose for long term oral contraception

### BACKGROUND OF THE INVENTION

In the majority of woman, the menstrual cycle lasts about 25 to 30 days. The menstrual cycle can be divided into two phases: (1) the follicular phase, at which time new follicles are recruited and their growth and development eventually lead to a single mature follicle; (2) the luteal phase, at which time the matured oocyte has been released and a new structure, the corpus luteum, is formed. In a typical cycle of 28 days, the follicular phase and the luteal phase are of equal length. During the cycle, the endometrial tissue responds to the changes of hormones such as, estrogen and progestin.

Menstruation signifies the beginning of a new menstrual cycle and the first day of menses is, by definition, counted as DAY ONE. During a span of about five to seven days, the superficial layers of the endometrium are sloughed because the demise of the corpus luteum is associated with a loss of progesterone secretion in the non-fertile menstrual cycle. Ovarian follicular maturation occurs resulting in a rise in the circulating levels of estrogen, which in turn leads to new endometrial proliferation.

At mid-cycle, the dominant ovarian follicle undergoes ovulation, which is induced by the gonadotropin surge, generally between menstrual cycle days 12 to 16 and is converted from a predominantly estrogen source to a predominantly progesterone source (the corpus luteum). The increasing level of progesterone in the uterus converts the endometrium from a proliferative phase to a secretory phase in which tissue proliferation has promptly abated, leading to the formation of endometrial glands or organs. When the released oocyte is fertilized and continues its progressive embryonic cleavage, the secretory endometrium and the conceptus interact to bring about implantation, beginning about 6 to 8 days after fertilization.

After fertilization, a process call "implantation" may occur, resulting in the

establishment of an ongoing pregnancy. First, the embryo will attach and burrow into the secretory endometrium and begin to produce human chorionic gonadotropin. The human chorionic gonadotropin in turn stimulates corpus luteum function and maintains an elevated progesterone level. In this case, menses does not occur in the fertile menstrual cycle. Pregnancy is then established. In contrast, in the non-fertile menstrual cycle, the waning level of progesterone in the blood causes the endometrial tissue to slough. This starts a subsequent menstrual cycle.

Since the implantation is a critical step for an impending pregnancy, more and more studies have shown that changes in the hormonal profile and uterine environment can prevent implantation, which in turn provides contraception. For example, estradiol is known to decrease gonadotropin release, such as follicle-stimulation hormone, by feedback inhibition. By the negative feedback loop, estradiol can also inhibit luteinizing hormone secretion. On the other hand, estrogen may also can cause a positive effect for the releasing of the gonadotropins. Increasing level of estradiol just before the ovulation cause the luteinizing hormone surge which is responsible for the final maturation and ovulation of the oocyte. Giving a woman high-doses estrogen immediately post-coitally also can prevent conception probably by interference with implantation.

A lot of physiological and clinical studies shown that administration of progestin makes the cervical mucus thick, tenacious and cellular. These changes in female reproductive system are believed to impede spermatozoal transport. Administration of progestin also inhibits luteinizing hormone secretion and blocks ovulation in humans. Therefore, progestins can also provide contraception.

Recently, The most used medication for oral contraception is a pill that has both an estrogen and a progestin component, a so-called combined oral contraceptive preparation. An alternative hormonal method of oral contraception is a pill that contains progestin only. However, such progestin-only preparations have a more varied spectrum of side effects than the combined preparations, an example being breakthrough bleeding. It is also less efficacious than the combined oral

contraceptives. As a result, the combined preparations are the preferred oral contraceptives in use today (Sheth et al., Contraception 25:243, 1982).

Today, the conventional 21 day pill packs with a 7 day "pill free" or placebo interval worked well when oral contraceptives were of higher dosage. However, as the doses decrease, for both the estrogen and progestin components, bleeding problems increase in frequency, especially in the early months of using of oral contraceptive, but even persistently so in some patients.

The clinical studies have suggested that decreasing the daily estrogen dosage will prevent the bleeding problems. Similarly, as the dosage of the progestin component was lowered, reduced androgenicity was also seen. Such changes in formulation have been presented in a variety of regimens, both mono-phasic and multi-phasic. Each has its own advantages and disadvantages. According to such improvements, today's oral contraceptives are much safer with regard to the incidence and severity of estrogen-linked clotting disorders and cumulative impact of more progestins in circulation.

Pat. No. 4,390,531 (U.S.) shows a tri-phasic medication in which each phase uses about 20-40 mcg ethinyl estradiol. The phases 1 and 3 use 0.3-0.8 norethindrone and phase 2 doubles the amount of the norethindrone. In a 28 day cycle, these three phases account for the first 21 days. In Pat. No. 0 226 279 (European) states that this regimen is associated with a high incidence of breakthrough bleeding and substitutes a three phase oral contraceptive medication using a relatively low amount of ethinyl estradiol (10-50  $\mu$ g) and a relatively high amount of norethindrone acetate (0.5-1.5 mg) in each phase provided that the amount of estrogen in any two phases is never the same. A pill-free phase of about 7 days is used in this regimen.

Pat. No. 5,098,714 (U.S.) describes an osmotic, oral dosage form. One pill is taken each day but the administration is, in effect, polyphasic. The dosage form is constructed such that it provides an initial pulse delivery of estrogen and progestin

followed by prolonged delivery of estrogen.

The Pat. No. 0 253 607 (European) shows a monophasic contraceptive preparation containing units having 0.008-0.03 mg of ethinyl estradiol and 0.025-0.1 mg of desogestrel and a medication where the preparation is administered over a 23-25 day period, preferably 24 days, followed by a 2-5 day of pill-free period. The object of this medication is to provide contraceptive protection and for hormonal replacement therapy the pre-menopausal woman in need thereof by supplying a low dose of an estrogen combined with a low dose of a progestogen.

In 1989, in USA, Food and Drug Administration and Maternal Health Drugs Advisory Committee recommends a low dose oral contraceptives for healthy, non-smoking women even during the perimenopausal years, such as ages 35-50. This decision is base on the review of accumulating data from the evolution of oral contraceptive pill formulations containing only 20-35  $\mu$ g of estrogen per day. In Japan, oral contraceptives are being evaluated for safety and efficacy, as well as social acceptability, for the first time.

Pat. No. 5,552,394 (U.S.) shows a female contraception method. The method is characterized by a reduced incidence of breakthrough bleeding after the first cycle which involves administering a combination of estrogen and progestin for 23-25 consecutive days of a 28 day cycle in a monophasic fashion. In this 28 day cycle, the daily amounts of estrogen and progestin are equivalent to about 5-35  $\mu$ g of ethinyl estradiol and about 0.025 to 10 mg of norethindrone acetate, respectively. In this method, the weight ratio of estrogen to progestin is at least 1:45, calculated as ethinyl estradiol to norethindrone acetate.

Two principal issues must be considered when establishing an estrogen-progestin regimen for oral contraceptives. First, the efficacy of the drug must be maintained and second, there must be avoidance of further worsening in the control of uterine bleeding. Clinical studies have shown that even commercially available oral contraceptive products have demonstrated efficacy but the overall incidence of

bleeding control problems has increased as the doses are reduced, as manifested both in breakthrough bleeding or withdrawal amenorrhea during the "pill free" week.

This is the objective of the current invention to provide a new estrogen-progestin combination and/or regimen for oral contraceptive use which maintains the efficacy and provides enhanced control of uterine bleeding. The medication enhances compliance by involving fewer stop/start transitions per year and also results in less blood loss in patients with anemia. Having fewer menstrual intervals can enhance lifestyles and convenience. The fewer "pill-free intervals" also should contribute to increased efficacy since they eliminate the intervals around which errors of compliance can occur and allow follicular development and occasional development of "dominant follicles" that cannot be corrected subsequently by the subsequent intake of estrogen / progestin tablets. This and other objectives of the invention will become apparent to those skilled in the art from the following detailed description.

## **SUMMARY OF THE INVENTION**

This invention describes a method of female contraception which is characterized by a reduced number of withdrawal menses per year. This is a new method of female contraception which involves administering, preferably in a monophasic fashion, a combination of estrogen and progestin for 180-364 consecutive days followed by 3-5 days of no administration, in which the daily amounts of the estrogen and progestin are equivalent to about 5-35 mcg of ethinyl estradiol and about 0.050-0.150 mg of levonorgestrel, respectively.

## **DESCRIPTION OF INVENTION**

In this new method of female contraception, a woman in need of contraception is administered a combined dosage form of estrogen and progestin, preferably in a monophasic fashion, for 180-364 consecutive days, followed by an administration-free interval of 3 to 5 days, preferably about 3 days. In this method the daily amounts

of estrogen and progestin are equivalent to about 5-35  $\mu\text{g}$  of ethinyl estradiol and about 0.050-0.150 mg of levonorgestrel, respectively. On a schedule of 180 days administration followed by 3 pill-free days, there are only two treatment and menstrual cycles per year.

Although other estrogens and progestins can be employed, the preferred estrogen is ethinyl estradiol and progestins is levonorgestrel. The weight ratio of these two active ingredients is at least 1:5. The preferable amount of ethinyl estradiol is about 10-20  $\mu\text{g}$  and the preferable amount of levonorgestrel is about 0.050-0.150 mg. Other estrogens vary in potency from ethinyl estradiol. For example, 30  $\mu\text{g}$  of ethinyl estradiol is approximately equivalent to 60  $\mu\text{g}$  of mestranol or 2,000  $\mu\text{g}$  of 17-beta-estradiol. However, other progestins vary in potency from norethindrone acetate. Thus, 1 mg of levonorgestrel is roughly equivalent to 3.5 mg of norethindrone acetate or 1mg of desogestrel and 3-ketodesogestrel, 0.7 mg of gestodene, 10 mg of TMG (Wyeth) or 2 mg of chlormadinone. The values given above are for the ethinyl estradiol and the norethindrone acetate and if a different estrogen or progestin is employed, an adjustment in the amount based on the relative potency should be made. The relative potency of the various estrogens and progestins are known.

Some estrogens cannot be used. These estrogens include the esters of estradiol, estrone and ethinyl estradiol such as the acetate, sulfate, valerate or benzoate, conjugated equine estrogens, agnostic anti-estrogens, and selective estrogen receptor modulators. The estrogen is administered in the conventional manner by any route where it is absorbed, such as orally or transdermally. Most of the estrogens are orally active and that route of administration is therefore preferred. The forms of administration of estrogen and progestin can be tablets, dragées, capsules or pills which contain the estrogen or progestin and a pharmaceutically appropriate carrier.

The pharmaceutical formulations, which contain progestin and a suitable carrier, can be solid oral dosage forms which includes tablets, capsules, cachets, pellets, pills, powders or granules; topical dosage forms which includes solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels or jellies,

foams and controlled release depot entities; and parenteral dosage forms which includes solutions, suspensions, emulsions or dry powder comprising an effective amount of progestin in this invention. The progestin, which is the active drug, can be contained in such formulations in addition to pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance. For example, "Modern Pharmaceutics", Banker & Rhodes, Marcel Dekker, Inc. 1979; "Goodman & Gilman's The Pharmaceutical Basis of Therapeutics", 6th Edition, MacMillan Publishing Co.; New York 1980 can be consulted.

The pharmaceutical formulations may be provided in kit form containing 28 active tablets to be taken once daily on successive days. The completion of one kit is immediately followed by the start of the next kit and the patient will take the tablets continuously for 180 to 364 days.

In order to further illustrate this invention, specific examples are described as following. However, these examples are for illustration only and are not intended to limit the scope of the invention.

#### **EXAMPLE 1**

A study is carried out at a fully accredited animal research facility which complies through its animal care and use committee with the review standards set forth in the National Institute of Health's "Guide for Care and Use of Laboratory Animals", the Public Health Services' "Principles for the Care and Use of Laboratory Animals", and the United States Department of Agriculture's Implementation Regulations of the 1985 Amendments for the Animal Welfare Act.

Ten adult female cynomolgus monkeys (*macaca fascicularis*) having regular presumably ovulatory menstrual cycles ( $28.9 \pm 3.1$  days for the month prior to study

entry) are selected. Their duration of spontaneous menses is 3.4+.1.4 days. Mean body weight of the monkeys is 4.9+.1.1 kg (X+.SEM). They are housed individually in a controlled environment (12 hours of light and 23.degree. C.). Their diet is a commercial primate food (Purina, St. Louis, Mo.) with water ad libitum.

The monkeys are divided at random into two groups (N=5 each). The studies begin with spontaneous menstruation in a pretreatment control cycle. At the onset of the next spontaneous menses, alternatively, they are assigned to receive on cycle day one an ultra low dose oral contraceptive for either 60 consecutive days, followed by 3 non-treatment days or 84 consecutive days, followed by a 7 non-treatment days. These regimens are continued through three treatment cycles. The study concludes with each group of primates being followed during a post-treatment spontaneous ovarian menstrual cycle.

Femoral blood is collected daily and the serum frozen for subsequent RIA of estradiol, progesterone, FSH and LH in the pretreatment and post-treatment cycles and every 3rd day during all three treatment cycles, except daily through the "pill free" interval. Bleeding profiles are kept by daily vaginal swabs, indicating spontaneous menstruation, withdrawal bleeding, breakthrough bleeding, or withdrawal amenorrhea. Breakthrough bleeding is defined as detectable blood in the vagina outside of the first 8 days after the last dose of oral contraceptive or the onset of spontaneous menses in non-treatment cycles.

Since the objective is to test an ultra low dose oral contraceptive, the medication is adjusted to fit the smaller (than human) body weight of these laboratory primates. The dose of ethinyl estradiol is 1.2 µg/day, while the dose of norethindrone acetate is 0.06 mg/day. This "in-house" reformulation is achieved by grinding to powder a commercially available monophasic pill (Loestrin 1/20, Parke Davis, Morris Plains, N.J.), which originally contained 1 mg of norethindrone acetate and 20 µg of ethinyl estradiol per tablet, contained in a conventional 21-day pack along with 7 iron-containing placebos.

In terms of comparison to human dose equivalents, the daily dose received by the

monkeys (with a monkey's body weight about 5 kg and a woman's at 50 kg) is about 12 µg of ethinyl estradiol and 0.6 mg of norethindrone acetate. Thus, this ultra low dose oral contraceptive formulation presented a 40% reduction in daily estrogen-progestin exposure as compared to one of the lowest estrogen dose combination oral contraceptives commercially available today in America or Europe. Taking into account that when a continuous 84-day ultra low dose regimen plus a 7-day pill free interval was used, versus the traditional 21 day protocol, that there would be 63 more doses on an annualized basis, still the exposure to medication was reduced by more than 26% yearly, compared to the commercial product Loestrin 1/20.

#### EXAMPLES 2-5

The example 1 procedure is repeated using the following combinations of estrogen and progestin:

Example	Treatment		Days
	Estrogen	Progestin	
2	mestranol	levo-norgestrel	84
3	17-beta-estradiol	3-keto-desogestrel	110
4	ethinyl estradiol	desogestrel	80
5	mestranol	gestodone	60

Application of the compounds, compositions and methods of the present invention for the medical or pharmaceutical uses described can be accomplished by any clinical, medical, and pharmaceutical methods and techniques as are presently or

prospectively known to those skilled in the art. It will therefore be appreciated that the various embodiments which have been described above are intended to illustrate the invention and various changes and modifications can be made in the inventive method without departing from the spirit and scope thereof.

**TABLE. Summary of Observed Days of Bleeding and/or Spotting and Bleeding<sup>29</sup>**

	<b>Bleeding and/or spotting</b>		<b>Bleeding only</b>	
	<b>Mean (SD)</b>	<b>Median</b>	<b>Mean (SD)</b>	<b>Median</b>
<b>Total observed number of days (364 possible days)</b>				
Seasonale	48.2 (44.0)	35.0	22.7 (22.8)	16.0
28-day OC	50.8 (27.0)	53.0	37.0 (19.6)	39.5
<b>Scheduled withdrawal bleeding</b>				
Seasonale (28 possible days)	10.6 (8.2)	10.0	7.9 (6.6)	7.0
28-day OC (91 possible days)	32.4 (18.2)	36.0	27.0 (16.3)	29.0
<b>Breakthrough bleeding</b>				
Seasonale (336 possible days)	37.6 (38.8)	26.0	14.8 (19.1)	7.0
28-day OC (273 possible days)	18.3 (17.2)	13.0	9.9 (11.9)	5.5

## References Cited

### U.S. Patent Documents

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<u>5098714</u>	Mar., 1992	Wright, et al..	
<u>5108995</u>	Apr., 1992	Casper	514/843.
<u>5208225</u>	May., 1993	Boissonneault et al.	514/843.
<u>5552394</u>	Sep., 1996	Hodgen.	
<u>5756490</u>	May., 1998	Lachnit et al.	514/843.

### Foreign Patent Documents

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8. Miller WB, Smith P. " Elimination of the Menses: Psychosocial aspects" J. Pschiat. Res. 1975; 12: 153-166
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### **Claims**

1. A method of female contraception which comprises monophasically administering to a pre-menopausal female a combination of estrogen and progestin for 180-364 continuous consecutive days in which the daily amounts of estrogen and progestin are equivalent to about 5-35 mcg of ethinyl estradiol and about .050 to 0.150 mg of levonorgestrel or its equivalents in progestin dose, respectively, following by non-administration for a period of 3-5 days maximum.
2. The method of claim 1 in which the daily amount of estrogen is equivalent to about 10 to 20 mcg of ethinyl estradiol.
3. The method of claim 2 in which the daily amount of progestin is equivalent to 0.050 to 0.150 mg of levonorgestrel.
4. The method of claim 3 in which the combination is administered for at least 180 consecutive days.
5. The method of claim 4 in which the estrogen is ethinyl estradiol.
6. The method of claim 5 in which the progestin is levonorgestrel or its equivalent progestin in appropriate potency dose.
7. The method of claim 1 in which the daily amount of progestin is equivalent to 0.050-0.150 mg of levonorgestrel.
8. The method of claim 1 in which the combination is administered for at least 180 consecutive days.
9. The method of claim 1 in which the estrogen is ethinyl estradiol.
10. The method of claim 1 in which the progestin is levonorgestrel.
11. The method of claim 1 in which the daily amount of estrogen is up to 30 mcg of ethinyl estradiol.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2004/000348

## A. CLASSIFICATION OF SUBJECT MATTER

IPC<sup>7</sup>: A61K31/56,31/565,A61P5/30,5/34

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Chinese Medical Abstracts, CNKI, CPRS

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNPAT, WPI, PAJ, CA, MEDLINE, CNKI, ethinylestradiol, levonorgestrel, 乙炔雌二醇, 左炔诺孕酮

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Ansbacher, R, Contraception, 2000 Dec, 62(6): 285-8, see abstract	1-11
X	Balogh, A et al, Contraception, 2000 Nov, 62(5): 259-69, see abstract	1-11
X	Jain, J.K et al, Contraception, 2000 Mar, 61(3): 195-8, see abstract	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2004/000348

### Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Claims 1-11 are directed to a method of treatment of human/animal body under PCT rules 39.1 and 67.1, but the search has been carried out and based on the OC combination of ethinylestradiol(EE) and levonorgestrel with low dose.

2. ☐ Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

### Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.